REMARKS/ARGUMENTS

By this Amendment, claims 6, 8-9, 17, 19-20, 28-29 are canceled, claims 4, 7, 10, 14, 18, 21, 23, 27, 30, 40, 42 are amended. Claims 1-5, 7, 10-16, 18, 21-25, 27, 30-61 are pending.

Favorable reconsideration is respectfully requested in view of the foregoing amendments and the following remarks.

Rejection under 35 USC 112 second paragraph

Claim 16, 34-46 and 51-61 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection is respectfully traversed.

Claim 16 recites the term "anti-solvent" which has indefinite metes and bounds because there is no definition for said term in the specification. It is unclear if this is another reagent, or a device, or a process. The Examiner argues that However, the specification does not describe what is considered an "anti-solvent". Thus, it is not clear from the claims or the specification what is used as an "anti-solvent" to cool, seed or partially remove solvent.

The Examiner argues that claim 16 recites the term "anti-solvent" has indefinite metes and bounds because there is no definition for said term in the specification, and alleges that it is unclear if this is another reagent, or a device, or a process.

In Hybri tech Inc. v. Monoclonal Antibodies, Inc., 231 USPQ. 81, 94 (CAFC 1986) it was stated:

> ". . if the claims read in light of the specification, reasonably apprise those skilled in the art both of the utilization and scope of the invention, and if the language is as precise as the subject matter permits, the courts can demand no more." (citing Shatterproof Glass Corp. v. Libbey Owens Ford. Co. 225 USPQ 634, 641 (CAFC 1985)).

Thus, whether a claim is in compliance with the second paragraph of § 112 requires a determination of whether those skilled in the art would understand what is claimed when the claim is read in light of the specification.

Here, the Specification discloses with regard to the term "anti-solvent" that (¶[0011]):

> Crystallization may be initiated by a method usually known in the art such as cooling, seeding, partial removal of the solvent from the solution, by adding an anti-solvent to the solution or a combination thereof.

Additionally, the Specification discloses with regard to the term "anti-solvent" that (¶[0015]):

> Forcible crystallization may be initiated by a method usually known in the art such as cooling, seeding, partial removal of the solvent from the solution, by adding an anti-solvent to the solution or a combination thereof.

Therefore, it is clear from the Specification that the anti-solvent is added to initiate or force crystallization of a solute from a solution. Accordingly, one skilled in the art would understand what is claimed when the claim is read in light of the specification.

The Examiner argues that claim 34 and claims dependent thereon recite the limitation of "activated tetrahydro-2-furoic acid' which is not clear how it differs from the usual tetrahydro-2-furoic acid. Applicant cites from the specification that "Activated tetrahydro-2-furoic acid refers to tetrahydro-2-furoic acid having its carboxylic acid group in a conventional activated form." Such an explanation does not clearly define the activated form is.

The Examiner argues that claim 34 and claims dependent thereon recite the limitation of "activated tetrahydro-2-furoic acid" which is not clear how it differs from the usual tetrahydro-2-furoic acid.

However, here the Specification discloses that (¶[0020]):

> Activated tetrahydro-2-furoic acid refers to tetrahydro-2-furoic acid having its carboxylic acid group in a conventional activated form.

Thus, one skilled in the art would understand what is claimed when the claim is read in light of the specification. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Rejection under 35 USC 102

Claim 1-8, 12-19, 21, 23, 34-36, 39, 41, 43, and 45-50 stand rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 4,315,007 (Manoury). This rejection is respectfully traversed.

The Examiner argues that both Examples I and II of the '007 patent yield the free base of alfuzosin. The Examiner sets forth that Example I teaches the crystalline form of alfuzosin base in particular, and Example II teaches the acid addition salt of said base, and therefore, the rejection is maintained.

In Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987) (MPEP 2131), the CAFC set forth that "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference". In the instant case, not every element of the claims is present in the '007 patent.

Here, the claims are directed to crystalline alfuzosin base, and contrary to the Examiners' argument, the Examples do not teach the isolation of crystalline alfuzosin base. Example 1, cited by the Examiner, refers to the crystallization of the hydrochloride salt, not the base ('007, column 3, lines 21-25):

> This yields a precipitate which is combined with the first and the whole is cyrstallised from a mixture of ethanol and ether. N_1-(4-Amino-6,7-dimethoxyquinazol-2-yl)-N_1-methyl-N_2-(tetrahydrofuroyl-2)-propylenediamine hydrochloride, which melts at 235°C (decomposition), is thus obtained.

Example II of the '007 patent referring to crystallization is directed to crystallization of alfuzosin hydrochloride ('007, column 4, lines 3-11):

> The residual amine is transformed into the hydrochloride in 2-propanol by addition of the theoretical amount of ethanolic hydrogen chloride. One obtains 1.84 g of the hydrochloride of N_1-(4-amino-6,7-dimethoxyquinazol-2-yl)-N_1-methyl-N_2-(tetrahydrofuroyl-2)-propylenediamine melting at 235°C. A mixed melting point test confirms identity with the product of Example 1.

The instant claims are directed to a crystalline form of alfuzosin base and processes for the preparation of crystalline alfuzosin base, which are not disclosed in the '007. In addition, the '007 patent does not teach crystalline alfuzosin base of a purity of 95% or 99%. Since the instant claims are directed to a crystalline form of alfuzosin base and processes for the preparation of crystalline alfuzosin base, which are not disclosed in the '007, the claims are not anticipated.

Accordingly, reconsideration and withdrawal of the rejection of the claims is respectfully requested.

Rejection under 35 USC 103

Claims 9-11, 20, 22, 24-33, 37, 38, 40, 42, 44 and 51-61 stand rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 4,315,007 (Manoury). This rejection is respectfully traversed.

The Examiner argues that the claims recite a process of crystallizing alfuzosin by using specific solvents such as: methyl-isobutyl ketone, methanol, ethanol which are not disclosed in Example I or II of Manoury. The Examiner argues that the solvents are within the same family as acetone, and isoamyl alcohol or 2-propanol.

The Examiner concludes that at the time of the invention, it would have been obvious to develop the claimed process because it would have been within the level of the skilled chemist in this art to substitute one ketone or alcohol for another in the same family of alcohols for optimum yield. The Examiner argues that such a modification is well within the level of the skilled chemist to obtain optimum yield. The Examiner concludes that the crystalline alfuzosin base and its HCl salt as well as the process of making them are obvious to one skilled in the art for the reason stated previously and for the explanation above.

However, the claims are patentable over the '007 patent for the following reasons. The framework for the objective analysis for determining obviousness under 35 U.S.C. § 103 is stated in Graham v. John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966). Obviousness is a question of law based on underlying factual inquiries. The factual inquiries enunciated by the Court are as follows: (A) Determining the scope and content of the prior art; and (B) Ascertaining the differences between the claimed invention and the prior art; and (C) Resolving the level of ordinary skill in the pertinent art. To establish prima facie obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. In re Royka, 490 F.2d 981 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." In re Wilson, 424 F.2d 1382, 1385 (CCPA 1970). MPEP 2143.03. It is important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does. (KSR v Teleflex, 12 S.Ct. 1727, 1740 (US 2007)).

Here, the claims are drawn to crystalline alfuzosin base, and a process for the preparation of crystalline alfuzosin base which comprises stirring a suspension of impure or noncrystalline alfuzosin base in a ketonic solvent selected from the group consisting of methyl ethyl ketone,

methyl isobutyl ketone, methyl isopropyl ketone, methyl tert-butyl ketone, and mixtures thereof or an alcoholic solvent selected from the group consisting of methanol, ethanol, tert-butyl alcohol and mixtures thereof.

However, there is not a reasonable expectation that different solvents would result in the formation of crystalline alfuzosin base because it is known in the art that the use of different solvents will produce different crystalline forms of a product. Banga et al. teaches (Banga S, Chawla G, Bansal AK. New trends in crystallization of active pharmaceutical ingredients. Business Briefing: Pharmagenerics 2004, 1-5 (Nov)) (pages 2-3):

> The concept that different crystalline modifications arise under varied experimental conditions demands the use of a diverse medley of crystallisation approaches to explicate the polymorph spectrum. Currently, the polymorph screen is a jumbled affair based mostly upon hit and trial bases. Crystallisation from solution (single solvent or solvent mixtures) and non-solvent methods such as sublimation, thermal treatment, desolvation, processing (grinding) and crystallisation from melting are the commonly used traditional approaches for polymorph screening. A meticulous consideration of the factors of solvent recrystallisation like solvent polarity, degree of supersaturation, temperature along with the cooling profile, additives, seeds, pH and agitation rate aids in elucidating the complete polymorphic picture of the drug.[9] However, the traditional crystallisation methods are exhausting, time-consuming and may be liable to miss metastable forms having an energy difference of less than 10kJ/mole, as observed in the case of paracetamol and chlorthalonil.[5] Therefore, innovative techniques allowing generations of 'crystal mutants' would prove to be of high value.

Therefore, the assumption that crystallization from different solvents will yield the crystalline alfuzosin base, has no basis in fact.

In addition, the Examiner has argues that one skilled in the art would be motivated to substitute one ketone or alcohol for another in the same family of alcohols for optimum yield, however, if the Examiner is aware of, or alleges to have some knowledge that there are cost

advantages to using the solvents as in the instantly claimed method, then the Examiner should provide such knowledge. It would not be appropriate for the examiner to take official notice of facts without citing a prior art reference where the facts asserted to be well known are not capable of instant and unquestionable demonstration as being well-known. For example, assertions of technical facts in the areas of esoteric technology or specific knowledge of the prior art must always be supported by citation to some reference work recognized as standard in the pertinent art. In re Ahlert, 424 F.2d at 1091, 165 USPQ at 420-21. If applicant adequately traverses the examiner's assertion of official notice, the examiner must provide documentary evidence in the next Office action if the rejection is to be maintained. See 37 CFR 1.104(c)(2). See also Zurko, 258 F.3d at 1386, 59 USPQ2d at 1697 ("[T]he Board [or examiner] must point to some concrete evidence in the record in support of these findings" to satisfy the substantial evidence test). If the examiner is relying on personal knowledge to support the finding of what is known in the art, the examiner must provide an affidavit or declaration setting forth specific factual statements and explanation to support the finding. See 37 CFR 1.104(d)(2).

Furthermore, there is no motivation for one of skill in the art to alter the methods of the '007 patent to arrive at the claimed method, and no reasonable expectation of success, because there is no teaching or suggestion within the '007 patent to arrive at the instantly claimed crystalline alfuzosin base. The Examiner argues that the motivation is the alleged expected benefit of substituting one ketone or alcohol for another in the same family of alcohols for optimum yield. However, the '007 patent does not disclose or suggest the substitution of different solvents for those disclosed, and furthermore, does not set forth any teaching or suggestion that the solvents will increase the yield. Since the patent does not disclose or suggest these limitations, there is no motivation to combine the references to reach these limitations, and no expectation of success.

Accordingly, reconsideration and withdrawal of the rejection of the claims is respectfully requested.

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For at least the reasons set forth above, it is respectfully submitted that the above-identified application is in condition for allowance. Favorable reconsideration and prompt allowance of the claims are respectfully requested.

Should the Examiner believe that anything further is desirable in order to place the application in even better condition for allowance, the Examiner is invited to contact Applicants' undersigned attorney at the telephone number listed below.

Respectfully submitted,

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Please charge or credit our Account No. 03-0075 as necessary to effect entry and/or ensure consideration of this submission.